

**University of Khartoum**  
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**Neural Tube Defects: Pattern, Incidence and  
short-term outcome in Omdurman Maternity  
Hospital, Sudan**

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بسم الله الرحمن الرحيم

قال تعالى :

اللَّهُ الَّذِي خَلَقَكُمْ مِّنْ ضَعْفٍ ثُمَّ  
جَعَلَ مِنْ بَعْدِ ضَعْفٍ قُوَّةً ثُمَّ جَعَلَ  
مِنْ بَعْدِ قُوَّةٍ ضَعْفًا وَشَيْبَةً يَخْلُقُ  
مَا يَشَاءُ وَهُوَ الْعَلِيمُ الْقَدِيرُ.  
صدق الله العظيم

سورة الروم الآية (54)

# **Dedication**

*This work is dedicated to my family who supported me all through and to all children of Sudan wishing them to be the happiest and healthiest on earth.*

# Acknowledgment

I would like to express my gratitude to my supervisor Dr. Salah Ahmed Ibrahim, Associate Professor and Head of the Department of Pediatrics and Child Health , who suggested the study and for his invaluable help and continuous guidance. I extend my thanks to Dr. Omer Elamin Kheir who supported me throughout this research.

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# **ABSTRACT**

In the developed countries, great improvement had occurred in the management of childhood illnesses which made the congenital diseases a major cause of infant morbidity and mortality, neural tube defects(NTDs) being one of them. In the last two decades a great effort has been done on NTDs leading to reduction in their incidence.

The objectives of this prospective hospital based study were to:

1) determine the incidence of NTDs in Omdurman Maternity Hospital 2) describe the spectrum of NTDs, 3) detect any associated congenital anomalies 4) assess the role of the sociodemographic factors, and 5) study the short term outcome of NTDs.

All babies born in Omdurman Maternity Hospital during the period from the 1<sup>st</sup> of February 2003 to the 31<sup>st</sup> of January 2004 with clinically detectable NTDs were examined and for each case consecutive normal birth was taken as a control. The surviving cases were followed up for the following three months.

The incidence of NTDs was 3.48/1000, 47.6% of the cases were myelomeningocele, 36.5% were anencephaly, 14.2% encephalocele and one

case was iniencephaly. Most of the cases were either stillborn or died in the early neonatal period. The male to female ratio was 1:5 and 20 % of the NTDs had other congenital anomalies . About 60% of the mothers were less <25 years of age and there was a significant association between NTDs and mother age (relative risk 2.3,  $p<0.0001$ ). Most of the parents of babies with NTDs had poor educational background , 54.8% of mothers had a significant history of previous stillbirth delivery. Only 30% of mothers had antenatal care. No mothers from the case or control group had used folic acid preconceptionally.

It is concluded that the incidence of NTDs in Omdurman Maternity Hospital is the highest in Africa and this invites a nationwide registry for all congenital anomalies and improvement in the obstetric services including active promotion of folic acid supplementation programs.

## ملخص الاطروحة

لقد حدث تقدم كبير في معالجة أمراض الطفولة في الدول المتقدمة الأمر الذي يجعل العيوب الخلقية من أهم أسباب أمراض ووفيات الأطفال وأحدها عيوب القناة العصبية. خلال العقدين الأخيرين تم عمل الكثير من الجهد مما أدّى إلى إحتواء وإنقاص نسبة حدوث مثل هذه العيوب.

**أهداف هذه الدراسة:** 1. تحديد نسبة عيوب القناة العصبية في مستشفى الولادة أمدردمان 2. معرفة نوعية هذه العيوب 3. الكشف عن وجود عيوب خلقية أخرى. 4. دراسة دور العوامل الاجتماعية والبيئية. 5. دراسة محصلة هذه العيوب بعد المتابعة.

تم إجراء هذه الدراسة في مستشفى الولادة أمدردمان في مدة عام كامل منذ بداية فبراير 2003م إلى نهاية يناير 2004م. تم استقصاء كل الأطفال الذين تم ولادتهم بعيوب القناة العصبية خلال هذه الفترة وتم متابعة الأحياء منهم لمدة 3 أشهر.

نسبة حدوث عيوب القناة العصبية 3.48 لكل ألف. ستون في المائة منها كانت حالات فتاق الظهر، 38% بدون رأس، 10% خروج كيس من الرأس، وحالة واحدة التحام الرأس مع الظهر.

ثمانون في المائة من هذه الحالات تم ولادتهم سقطاً أو توفوا خلال الشهر الأول من الولادة. نسبة الذكور إلى الإناث كانت 5:1، 20% من الحالات صاحبته عيوب خلقية أخرى. ستون في المائة من الأمهات كن أصغر من 25 سنة، 60% من الآباء والأمهات كانت درجة تعليمهم منخفضة، 57.8 من الأمهات كان لديهن تاريخ ولادة طفل ميت كما أن 30% فقط من الأمهات كن يتابعن أثناء الحمل. كل الأمهات لم يستعملن حامض الفوليك قبل الحمل.

خلص البحث إلى أن نسبة حدوث عيوب القناة العصبية في مستشفى الولادة أمدردمان هي الأعلى في أفريقيا وهذا يستلزم عمل تسجيل لكل العيوب الخلقية وتحسين الخدمات التي تقدم للنساء قبل الولادة وتنظيم برامج للتوعية بأهمية أخذ حامض الفوليك قبل الحمل.

## List of Abbreviations

AFACHe	Amniotic fluid acetylcholine esterase
AFAP	Amniotic fluid alpha feto protein
CDC	Center for Disease Control and Prevention.
DNA	Deoxy ribonucleic acid`
LDDM	Insulin dependant diabetes mellitus
LSCS	Lower segment cesarean section
MSAFP	Maternal serum alpha fetoprotein
MTHFR	Methylene tetra hydro folate reductase
NND	Neonatal deaths
NTDS	Neural tube defects
J/S	Ultra sound
USA	United States of America
USPHS	United States Public Health Services.



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# **1. NEURAL TUBE DEFECTS**

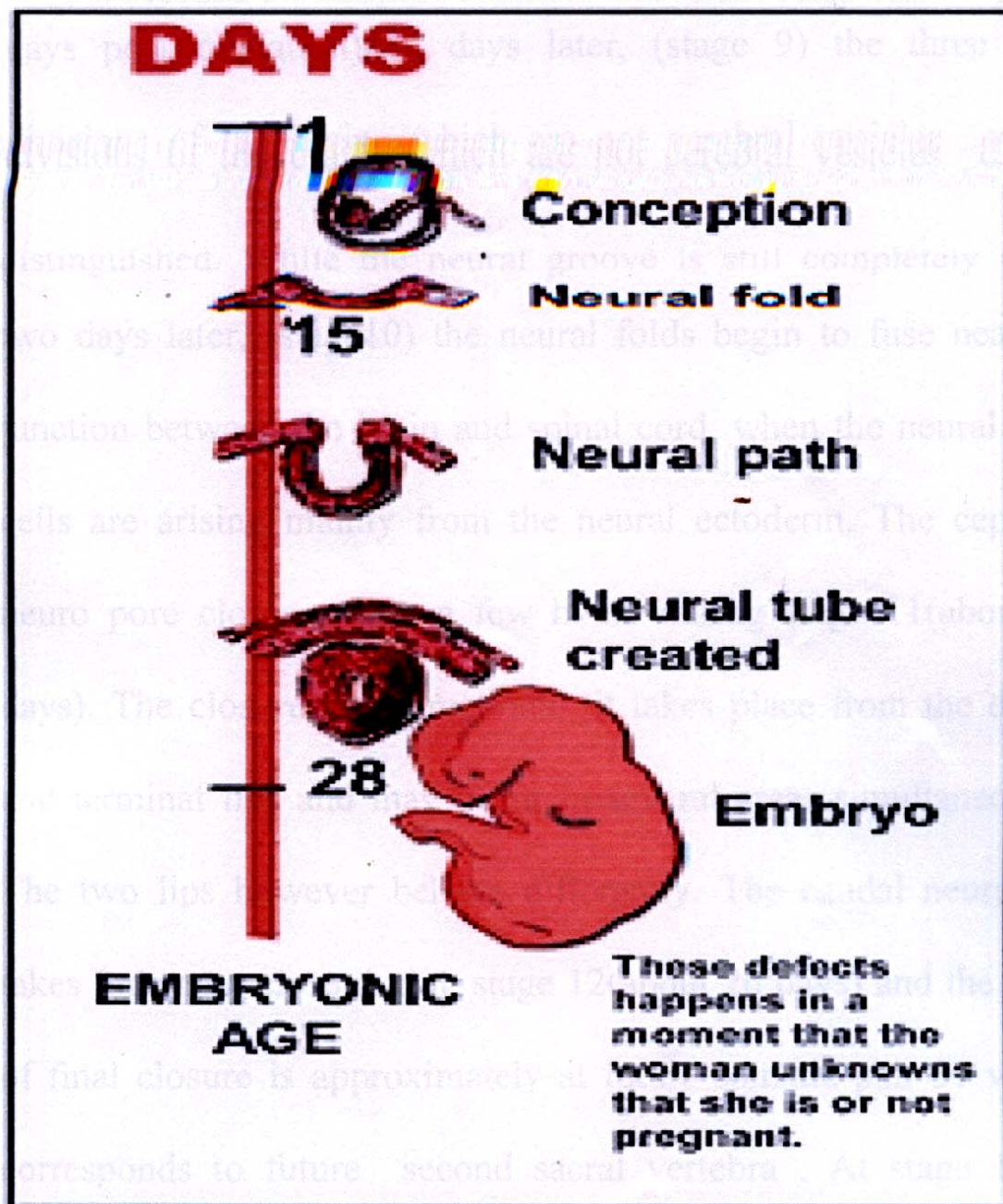
## **1.1. Definition:**

Neural tube defects (NTDS) are congenital structural abnormalities of: the brain, skull and spinal cord. They arise during the first 28 days of gestation when the neural tube is forming. They can be isolated (commoner) or arise as part of a syndrome (syndromic). Syndromes known to contain NTDs include Meckel-Gruber, Robert, HARDES, the trisomies 13, 18, and Down syndrome.

They are a major cause of stillbirth, neonatal and infant deaths or severe lifelong handicaps (1).

## **1.2. Embryology of the neural tube:**

Figure A: simplifies the steps of neural tube formation in utero.



**Fig A Steps of Neural tube formation. (Reproduced from Grays and Harley book of Anatomy 1927)**





The neural groove and folds are first seen during stage 8 (about 18 days post ovulation) two days later, (stage 9) the three main divisions of the brain which are not cerebral vesicles can be distinguished. While the neural groove is still completely open, two days later, (stage 10) the neural folds begin to fuse near the junction between the brain and spinal cord, when the neural crest cells are arising mainly from the neural ectoderm. The cephalic neuro pore closes within a few hours during stage 11 (about 24 days). The closure is bidirectional; it takes place from the dorsal and terminal lips and may occur in several areas simultaneously. The two lips however behave differently. The caudal neuropore takes 9 days to close during stage 12 (about 26 days) and the level of final closure is approximately at future somatic pair 31 which corresponds to future second sacral vertebra . At stage 13 (4 weeks) the neural tube is normally completely closed (2).

### **1.3. Classification:**

#### **NTDs are classified as**

- i. Open: when either the membranes or the neural tissue or both are exposed to the amniotic fluid.
- ii. Closed: when either of the above is covered with skin. NTDS are further subclassified as:

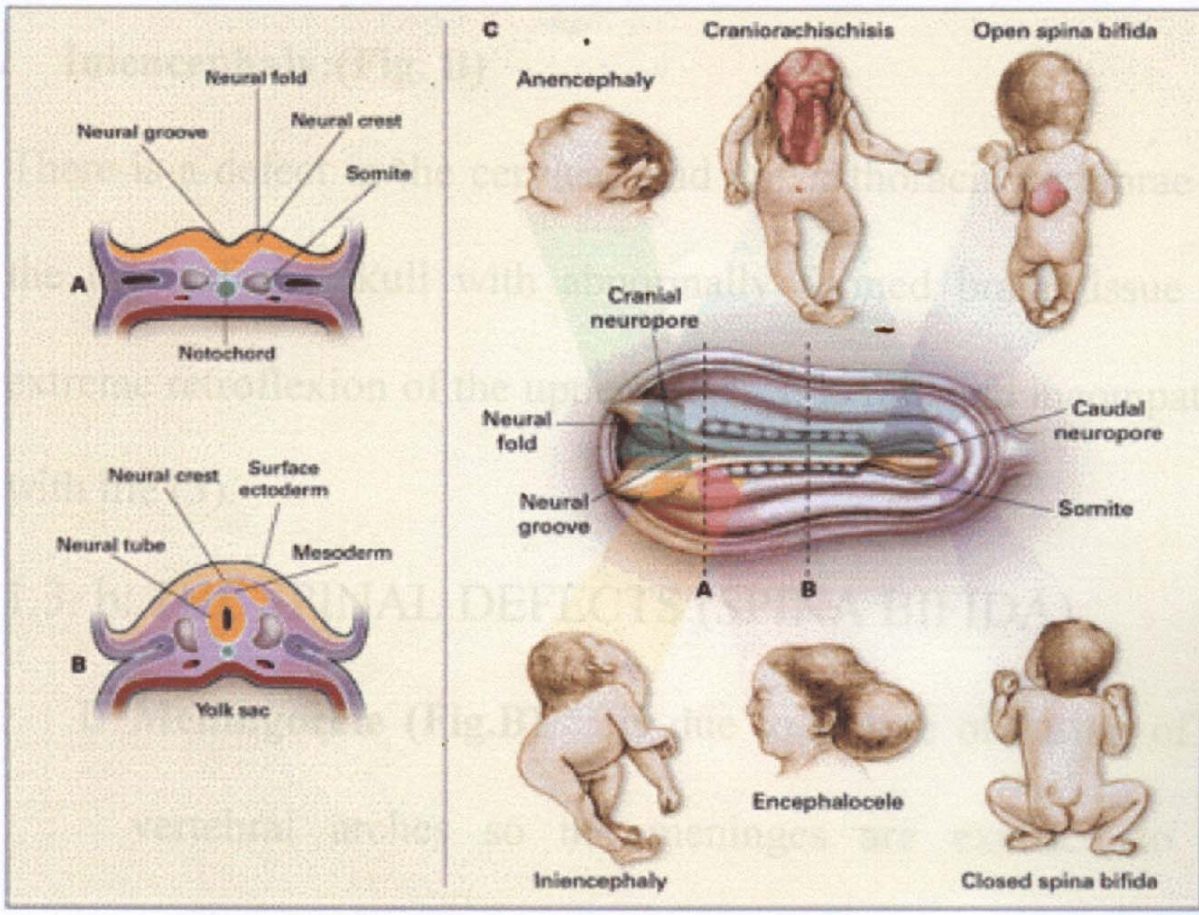
### **1.3. a: CRANIAL DEFECTS**

#### **i. Anencephaly:(Fig. B)**

This is the most severe and second commonest form. Here the fore- brain, meninges, vault of the skull, and the scalp fail to form.the condition is incompatible with life leading to stillbirth delivery or early neonatal death (3)

#### **ii. Exencephaly (craniorachiasis) (Fig.B)**

Here there is failure of scalp and skull formation with protrusion of abnormally formed brain. It is rare and incompatible with life (3).



**Fig B: Types of Neural tube defects. (Reproduced from Grays & Harley book of Anatomy 1927)**

### **iii. Encephalocele (Fig. B)**

This comprises 10% of NTDs .There is extrusion of brain tissue through a defect in the skull (3).

### **iv. Iniencephaly:(Fig. B)**

There is a defect in the cervical, and upper thoracic vertebrae and the base of the skull with abnormally formed brain tissue and extreme retroflexion of the upper spine. It is rare and incompatible with life (3).

## **1.3. b: THE SPINAL DEFECTS (SPINA BIFIDA)**

I. Meningocele (Fig.B) :is due to failure of fusion of the vertebral arches so the meninges are exposed to the amniotic fluid (3).

### **II. Myelomeningocele(Fig. B):**

Failure of fusion of the vertebral arches with protrusion of both the meninges and the neural tissue to the amniotic fluid. The neural tissue is damaged by such exposure and accordingly the structures supplied by the damaged nerves will be nonfunctioning.e.g lesions of the lumbosacral area cause paraplegia + bowel and bladder dysfunction .Higher lesions affect more structures and thus cause more handicap.

Open spinal defects are associated with ventriculomegaly or hydrocephalus.

#### **1.4: Burden of suffering:**

NTDs cause substantial morbidity and mortality .Anencephaly and the other cranial defects are almost always lethal. Spina bifida can range from mild (closed spina bifida) to severe form (open myelomeningocele).

Aggressive surgical and medical cares are always required for the severe form. Special schooling and rehabilitation are needed for the patients with permanent disabilities. Based on 1988 cross — sectional data, the estimated life time cost of spin bifida is \$25 8.000 per case. (4)

#### **1.5: Risk factors:**

##### **a. Familial:**

Neural tube defects can run in families; parents with affected children have increased chance of having another one with the defect and the incidence increases with increasing family history (0.3% when no family history to 43% when either both parents have NTD or there are two previous children with NTD (5).

Genetically: many studies were done to disclose why some persons are more prone to be affected by NTDs than others and hence why do NTDs run in some families. These studies demonstrated that the condition is due to mutations in the enzyme (MTHFR) gene, the known mutation now is the

→

677C T mutation and only one copy is needed for the expression of this gene making the person vulnerable to NTD(5-7).

There are additional folate-related genes that contribute to NTDs occurrence including mutant forms of folate receptors such as FRalpha. Genetic association between molecular variants of the FRalpha gene and NTDs have been documented suggesting that this gene may be a risk factor for human NTDs (5). These genetic studies may explain why certain ethnic groups are more vulnerable to NTDs than the others. However, more than 90% of NTD cases occur with no previous family history (5-7).

#### **b. Diet:**

Folic acid deficiency is now known to be associated with high incidence of NTDs (7).

#### **c. Certain diseases:**

There are certain diseases that are known to be associated with NTDs in the offspring like insulin dependant diabetes mellitus(IDDM) and hypothyroidism.

#### **d. Drugs:**

Drugs such as anti convulsants e.g. valproic acid anti malarials

e.g. Fansidar; these act as antifolates and antagonize the action of folate in intermediary metabolism (8).

**e. Maternal hyperthermia:** during the first trimester is reported to cause NTDs although the mechanism is not known (8).

### **1.7 Incidence:**

**Globally** 500.000 children are born each year with NTDs.

The highest incidence reported was in a rural area in northern **China** where the incidence was 6/1000 before the supplementation of women in the child bearing age with folic acid when the incidence dropped to 2/1000 (9). In the **USA** the incidence now is 1/1000 after the nationwide fortification of diet with folic acid and NTDs are more prevalent among the Hispanic and non-Hispanic whites compared of the Blacks, and predominantly in the younger age group of mothers (10).

In **Europe**: the incidence was highest in **Ireland** among the Celtic population, it was 4/1000 (11). In Canada the incidence dropped from 16.4/10.000 to 8.6/10.000 after fortification of diet with folic acid (12).

#### **1.7.1. Incidence and prevalence in Africa:**



**Malawi 2000:** The incidence of spina bifida in one central hospital was 0.47/1000(13).

**Tunisia 2000- 2001:** The incidence of encephalocele is 0.25/1000 and the females are affected more than the males. It is associated with other malformations like : facial(20%) skeletal (17%) and renal system (3%) (14). The incidence. of spina bifida was 1.05/1000 (15).

**Cape Town (South Africa 1994):**

The prevalence of NTDs was 1.74/1000; the highest rate was among the whites more than the blacks, and NTDs affected female babies more than males (16).

**Ghana: (1991-1992):** the prevalence was 1.15/1000, anencephaly was 73% and spina bifida 27 %( 17).

**Congo: 1993:** The incidence of anencephaly was 0.12/1000 and the suggested cause for the occurrence of spina bifida was the consumption of a type of potatoes infected with phytophthora infestation (18.).

**1.7.2: Neural tube defects and Sudan:**

No study has been done in Sudan focusing on NTDs. In the study done on hydrocephalus in Sudan by Ibrahim Abdelaziz in a 4 year period from 1971

to 1974, out of 101 cases of hydrocephalus there were 4 cases with meningocele (19). From the hospital records in Omdurman Maternity hospital, the number of spina bifida cases admitted to the neonatal care unit had increased during the last three years, no cases were admitted in the year 2000, 13 cases were reported in 2001 and 33 cases in 2002.

### **1.8. Screening and prenatal diagnosis:**

This is offered mostly to women at risk of having an NTD pregnancy. NTDs can be detected in utero by the following methods:

- i. Measurement of maternal serum alpha fetoprotein (MSAFP)
- ii. Ultra sound scanning.
- iii. Amniotic fluid acetylcholine esterase (AFAchE).
- iv. Amniotic fluid alpha fetoprotein (AFAP).

The latter two are used primarily as confirmatory tests and are not regarded as part of the routine screening of women at risk (20).

#### **1.8.1MSAFP:**

This is measured at 16-18 weeks of gestation. It is a good predictor of NTDs. Depending on the cut off level used to define an elevated level (usually 2-2.5 times the median value for gestational age reported as multiples of the median MoM), screening can detect between 56%-91% of affected fetuses (20). An elevated MSAFP occurs in 1-5% of pregnant women but for a

number of reasons the likelihood of an NTD giving a positive screening result is small for the following reasons:

First: above one third of positive results are not confirmed by a second MSAFP (i.e false positives) second : although the reported sensitivity of MSAFP when followed by appropriate diagnostic u/s. AFAP approaches .100 % MSAFP tests are not specific: there are other conditions that can cause high MSAFP they include: under estimated gestational age, other congenital anomalies like anterior abdominal wall defects, multiple gestation etc. These false positive results are ruled out by u/s or (if u/s was not informative) by amniocentesis (to measure AFAFP and AFACH<sub>E</sub>) (20).

In comparison to the number of women who must be tested the number of NTDS detected by amniocentesis is small (0.06- 0.16%). That is because more than 90% of NTDs occur in women with no previous risk (20).

### **1.8.2 Ultrasound scan:**

All cases of anencephaly can be detected by U/S alone as can many closed neural tube defects that escaped detection by MSAFP measurement current ultrasound techniques are less sensitive in detecting other NTDs like small meningoceles; so U/S scanning needs appropriate machine and expert training to avoid under or over diagnosis of NTDs. In centers where there is

appropriate machines and expert trainee the specificity of U/S scanning reaches 100% (20).

### **1.8.3 Benefits of screening:**

The benefits of prenatal screening are:

**a) to inform prospective parents** of the likelihood of carrying an NTD pregnancy. Parents may be counseled about the consequences of the malformation and can make decisions about keeping it or preparing the optimal care for their future baby or choose to have elective abortion ;for example, the prenatal diagnosis of anencephaly can spare parents some of the trauma associated with delivering such malformation (20).

**b)Induced abortion is sought** by the majority of women in the United Kingdom where screening by MSAFP and U/S are widespread. It is reported that there was 49-50% decline in the birth prevalence of anencephaly and 32-38% decline in spina bifida rates attributable to elective abortions (20).

The effectiveness of reducing the prevalence of NTDs by screening and early detection is limited by the universal acceptance of screening and the cultural and religious backgrounds concerning acceptance of abortion (21).

### **1.8.4: Potential risks of screening:**

The most important risks include ;1) the risk to the fetus from amniocentesis,2) the psychological effects on the parents of positive results,3) the complications of induced abortion. and 4) the risks of elective abortion.

**i.Risk to the fetus from The amniocentesis :**

This include: miscarriages, puncture to the fetus, bleeding, infection and possibly isoimmunisation .the procedure related rate of fetal loss with current technique is about 0.5-0.8% (22).

**ii.Psychological effect on the parents of a positive test:**

This is especially important because the large majority of positive screening tests in low risk mothers are false positives. There is statistical evidence that expectant parents with normal fetuses suffer a great deal of anxiety while awaiting confirmatory tests (22).

**iii. The potential complications of induced abortion:**

The maternal case fatality rate from legally induced abortion is 0.4/100.000 procedures.

**iv. The induced abortion of a normal fetus:**

This is a very serious consequence of false positive results, but appears to be very uncommon with current diagnostic techniques. Investigators

have reported false positive results leading to elective abortion of normal fetuses to be less than 0.006 -0.007 % of women screened (22).

### **1.9: Prevention:**

It is now well proven that folic acid deficiency is closely related to NTDs occurrence. A number of large population based studies associating maternal folate deficiency with NTDs serve as the scientific basis for prevention by folic acid(21-23).

#### **1.9.1 What is folic acid/.folate?:**

Folate is a member of the water soluble vitamin B complex; folic acid is the synthetic form of it.

#### **1.9.2: Foods rich in folates:**

Vegetables, cabbage, cauliflower, English spinach, green beans, grapefruits, orange, soya beans, lentils, haricot beans, eggs, peanuts, many apples and orange juices. Folate is an inclusive term for biologically active forms of pterylglutamic acid (23).

#### **1.9.3: Role of folates in intermediary metabolism:**

Naturally occurring folate include dihydro and tetra hydro folate and may have up to seven additional glutamic acid residues. Synthetic folic acid is an oxidized form with one glutamic acid residue; it must be oxidized to

tetrahydrofolate to be biologically active. Dihydrofolate is an important co-factor for metabolic reactions modify organic molecules by adding or removing a single carbon (methyl) unit; these reactions are essential for DNA synthesis and cell division. These reactions are rate limited by the enzyme methylenetetrahydrofolate reductase (**MTHFR**) which catalyses the conversion of homocysteine to methionine. Homocysteine accumulates if conversion to methionine is slowed because of shortage of folates or inherited enzyme variants. A raised homocysteine suggest suboptimal nucleic acid and amino acids metabolism. It also has a direct atherosclerotic effects on the blood vessels and hence increasing the possibility of vascular diseases and stroke and may increase the risk of certain cancers and dementia (23, 24).

#### **1.9.4: Methods of prevention by folic acid:**

The recommendation now is to take folic acid preconceptually i.e. before the woman try to get pregnant. In 1992 ,the United States Public Health Service (USPHS) recommended that all women in the child bearing age should consume 400 micrograms of folic acid on an ongoing basis to reduce the risk of having a pregnancy affected by NTDs This recommendation was preceded a year before by the recommendation of the Center of Disease Control and Prevention (CDC) for women at high risk (women who had an

earlier pregnancy affected with NTD) to consume 4.000 micro gram of folic acid from the time they try to conceive through the first trimester of pregnancy to reduce the risk of having a NTD (25).

### **Why should folic acid be taken preconceptionally?:**

Because the neural tube formation occurs in the first 28 days of gestation even before the woman recognizes that she is pregnant (26).

### **1.9.5:Ways of achieving increased folic acid consumption:**

There are many ways do this:

- a. By increasing the consumption of foods rich in naturally occurring folates.
- b. By increasing the use of folic acid containing pills before conception.
- c. By fortification of a staple food stuff (e.g. flour, sugar. etc) with folic acid.

In 1998 the CDC in U.S.A mandated a nationwide fortification of enriched grain products with folic acid (the synthetic form of folates).

The food and drug administration (FDA) chose to require a concentration of folic acid that increase women consumption by 100 microgram /day, the concentration required was 140 microgram of folic acid /100 gram of grain or 1.4 parts/1 .000.000 (27-30).



Other countries that mandated fortification with folic acid include: Canada (1998) Chile and some other Countries In the Americas. Selected foods are also fortified in Hungary (31).

#### **1.9.6: How much is folic acid fortification effective:**

Folic acid proved to be effective in preventing NTDs. In a 1999 study, the CDC reported its results of a randomized control trial of folic acid use preconceptually in a rural area in Northern China Where the incidence was 6/1000, women took 400 microgram daily from the time of their premarital examination until the end of their first trimester of pregnancy , the incidence dropped to 1/1000. In the U.S.A: the incidence dropped by about 50 % (31)

#### **1.9.7 Fortification in contrast to supplementation:**

Supplementation is effective but it depends on the women awareness of the importance of folic acid, their level of education and cultural influences. At sufficiently high serum/plasma folate concentrations (adequate) homocysteine concentrations are reduced and there is a linear increase in homocysteine concentrations as folate levels decline (32).

### **1.9.8 Other beneficial effects of folic acid supplementation:**

Many studies have proved that folic acid prevents the occurrence of atherovascular disease like heart attacks and strokes, some cancers like cancer of the colon and pernicious anemia caused by folate deficiencies. Homocysteine has direct atherosclerotic changes to the blood vessels increasing the chance of strokes and heart attacks and since homocystiene is inversely related to folate, so increasing consumption of folic acid decreases the occurrence

of these conditions. A large multi center European study published in 1997 concluded that consumption of a simple multivitamin pill containing folic acid is associated with a strong protective effect- a statistically significant (62%) reduction in atherovascular disease (33). Folate deficiency causes mutations in DNA synthesis and so can play a role in colonic cancer hence folate supplementation reduces the risk of this cancer by 75 % (34).

**Justifications:**

- Neural tube defects cause significant morbidity and mortality in children.
- Few studies have been done focusing on neural tube defects in Sudan.
- Prevention of neural tube defects is cost effective while management of residual damage and handling of complications is costly and tasking.

**Objectives:**

The objectives of the study were to:

1. Determine the incidence of NTDs in Omdurman Maternity Hospital.
2. Describe the spectrum of NTDs.
3. Detect any associated congenital anomalies.
4. Assess the role of sociodemographic factors.
5. Study the short term outcome of NTDs.

## **2. MATERIALS AND METHODS**

### **2.1: Study design:**

The study was a prospective hospital based case-control study.

### **2.2: Study area:**

The study was conducted in Omdurman Maternity Hospital; this is one of the biggest hospitals in the country and the first hospital specialized in obstetric care. The nucleus of the hospital as a midwifery school was founded in 1921 in Omdurman City which is considered to be the national capital of Sudan and is inhabited by about three million people of different ethnic groups and coming from all parts of the country. The hospital has a very high delivery rate between 15.000-18.000 delivery per year. It has also got a neonatal care unit which accepts about 100-120 neonate per month. The Obstetric Department consists of: an Emergency Department with the labour room accepting about 60-100 delivery per day, two theatres, referral clinics for antenatal care and follow up, ultrasound department as well as the well recognized midwifery school.

### **2.3: Study duration:**

A one year study: 1st February 2003- 31st January 2004

### **2.4: Study population:**

All infants (live birth and still birth) born in Omdurman Maternity Hospital during the study period.

## **2.5: Sample size:**

$$N = Z^2 (p_1 \cdot q_1 + p_2 \cdot q_2) / d^2$$

$$N = (1.96)^2 (0.5 \times 0.5 + 0.5 \times 0.5) / 0.02^2 = \mathbf{70}$$

N=sample size

Z=statistical certainty

P1=probability of success in case finding.

q1= probability of failure in case finding.

p2= probability of success in control finding.

q2=probability in failure in control finding.

## **2.6: Inclusion criteria:**

### **2.6.1: Study group:**

Babies (livebirth & stillbirth) born in Omdurman Maternity Hospital with clinically detectable NTDs.

**2.6.2: Control group:** The nearest subsequent baby delivered after the case was taken as a control. The number of the controls was double the cases.

## **2.7: Exclusion criteria:**

Babies excluded from the study were:

Babies born outside the hospital.

Babies whose their parents refused to participate in the study.

## **2.8: Research technique:**

### **2.8.1: Consent:**

An informed consent was obtained from the parents to include them in the study and to take photographs for the NTD cases. A written consent was obtained from the hospital administrator.

### **2.8.2. Research tools:**

**I. Questionnaire:** A structured questionnaire sheet was used to collect data from the mother including informations about personal data, socioeconomic, medical and obstetric histories, the use of folic acid and mode of the delivery.

**II. Examination sheet:** This is completed after examining the newborn and included:

a) gestational age assessment using Parkin method.

b) general examination with search of any other congenital anomaly.

- c) anthropometric measure: using a non-stretchable plastic tape & measurements of head circumference and length were taken to the nearest centimeter.
- d) description for the NTD with its location.
- e) reporting of any neurological complication.

### **III. Follow up sheet:**

The surviving cases were followed up for three months to report on the short term outcome (surgery, complications, death... etc)

#### **2.8.3: Research team:**

- a. The author: the team leader who trained the other members of the research team in identifying the NTD cases, completing the questionnaires, examining the affected newborns, and the controls.
- b. One house officer: His role was to stay in the labour room and report any NTD case.
- c. Two midwives from the labour room: Their job was to identify the NTD cases and to inform the doctor about them and complete the maternal data. (An Arabic questionnaire was used).



- d. One nurse from the Neonatal Care Unit: her role was to complete the questionnaire for NTD case admitted to the Unit.

#### **2.8.4 Verification of data:**

The author participated in completion of questionnaire and verified the data filled by the research team depending on the stay of the cases in the hospital.

### **2.9: Data Analysis:**

- The data was entered in the computer using the soft ware, Fox Pro.
- Simple descriptive statistics, frequency distributions and cross tabulation were done using Epiinfo program (version 6).
- Results were tested for significance using Odds ratio to calculate the relative risk (RR).  $X^2$  and Fisher Exact tests were used; a probability of  $< 0.05$  was considered to be significant.

### 3. RESULTS

Through out the study period from the first of February 2003 to the end of January 2004 in Omdurman Maternity hospital, 18378 deliveries were recorded.

#### 3.1: Incidence of Neural tube defects:

**Table 1.** Describes the incidence of NTDs compared to other congenital anomalies at birth. The incidence of NTDs was **3.48/1000** .me incidence of other congenital anomalies at birth was 2.34/1000 and the incidence of all congenital anomalies including NTDs was 5.82/1000 thus :NTDs constituted 59.4% of all congenital anomalies at birth.

#### 3.2: Spectruth and outcome of neural tube defects:

As shown in **Table2** and **Figure 1**: the most frequent NTD was the myelomenigocele (Fig. C), seen in 30 cases (47.6%), followed by the anencephaly (Fig. D), in 23 (36.5%) cases and then the encephalocele in 9 (14.2%)

**Table 1. Incidence of neural tube defects (NTDs)**

Total NTD's Feb 03 to Jan04	63
Incidence of NTD's	3.48
(recognized at birth per 1000 deliveries)	
Incidence of other congenital abnormalities	2.34
(recognized at birth per 1000 deliveries)	
Total incidence of congenital abnormalities	5.82
(recognized at birth per 1000 deliveries)	
NTD's as a % age of all congenital anomalies	59.4%
(recognized at birth)	



**Fig C: A Case with open myelomeningocele**



**Fig D: A case with anencephaly**



## **Fig E: A Case with Iniencephaly**

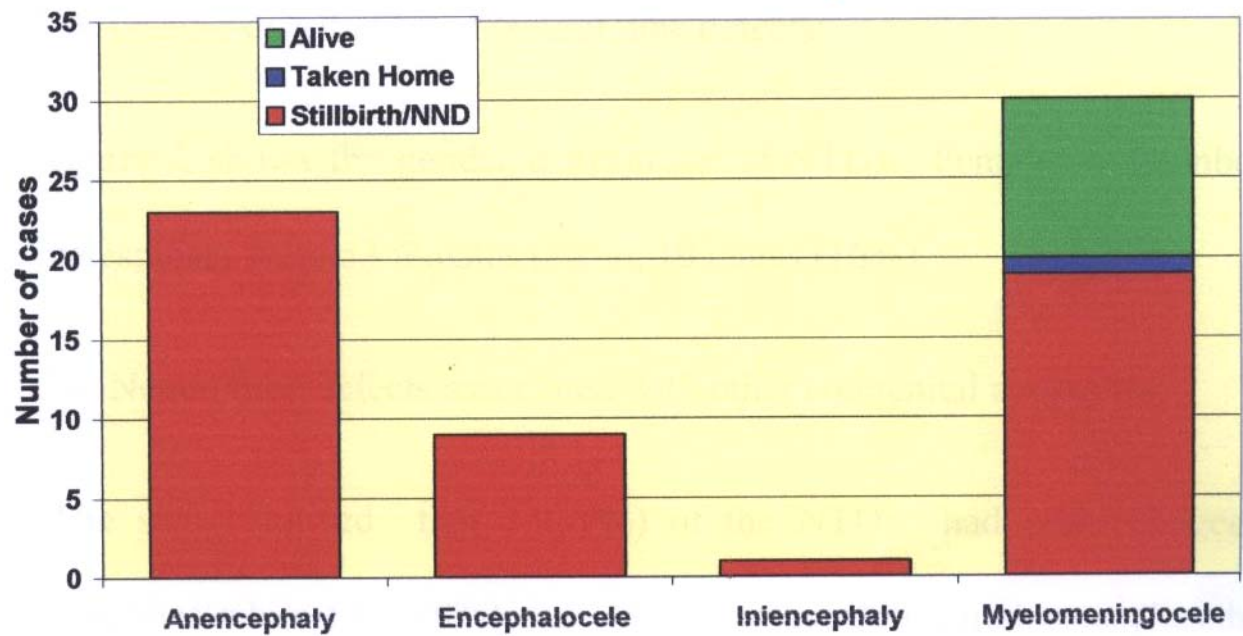
**Table 2: Spectrum of NTDs**

NTD	Total	Still birth/NND	Alive	Taken home
Anencephaly	23	23	0	0
Encephalcoele	09	09	0	0
Iniiencephaly	01	01	0	0
Myelomeningocele	30	19	10	01
<b>Total 63</b>	<b>52</b>	<b>10</b>	<b>1</b>	

**NTDs = Neural Tube Defects**



**Figure 1: SPECTRUM AND OUTCOME OF NTDS**  
(n=63)



cases. A rare NTD (that is the iniencephaly (Fig. E)) was found in one case (1.5%).

Regarding the outcome, most of the cases (n=52, 82.5%) were either stillborn or died within the neonatal period, only 10(15.9%) cases survived and one case was taken against medical advice.

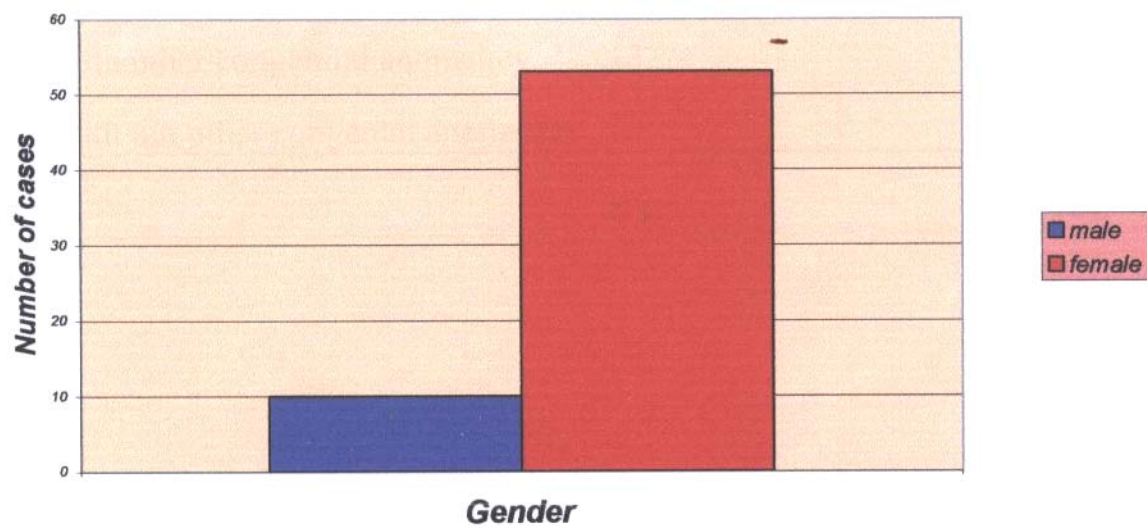
### **3.3: Gender distribution of Neural tube defects:**

**Figure 2** shows the gender distribution of NTDs Females outnumbered males; there were 53 females (84%), 10 males(16%).

### **3.4. Neural tube defects associated with other congenital anomalies:**

The study showed that 13(20%) of the NTDs had other congenital anomalies while 53 (80%)cases had no other congenital anomalies.these congenital anomalies were:cleft lip and palate (3cases), club foot (2 cases oexomphalos(1 case),genital prolapse (1case),accessory nipple with undescended testes (1case,enophthalmos with club foot (1 case),poly dactyly with palpable kidney and deficient abdominal wall (1 case).

**Fig. 2: Gender distribution of NTDS**



**Table 3: Cases and other congenital anomalies. (n63)**

	No	%
Cases with other congenital anomalies	13	20
Cases with out other congenital anomalies	50	80
<b>Total</b>	<b>63</b>	<b>100</b>

### **3.5. Maternal age:**

It is shown in **Table. 4** and **Figure 3** that most of the mothers (n=55, 55.6%) of babies with NTDs were in the younger age group: from 15 -24 years, and the relative risk was 2.3 i.e. the mother had 2.3 times the chance of having an NTD baby when she is below 25 years of age which is strongly statistically significant ( $p < 0.0001$ ) This is in contrast to the control group where most of the mothers (n=92, 74.8%) were more than 25 years of age.

### **3.6. Maternal and Paternal Educations:**

**Table 5** and **Figures 4** and **5**: shows that most of the mothers had poor educational background i.e. 48% had basic education and 27.4% were illiterate. This applies also for the fathers. In contrast most of the parents in the controls had higher secondary school education (32.3%) and the illiterate were 6.1% and basic (28.2%) groups and the percentage of university educated is recognizably higher i.e. 23.4%.

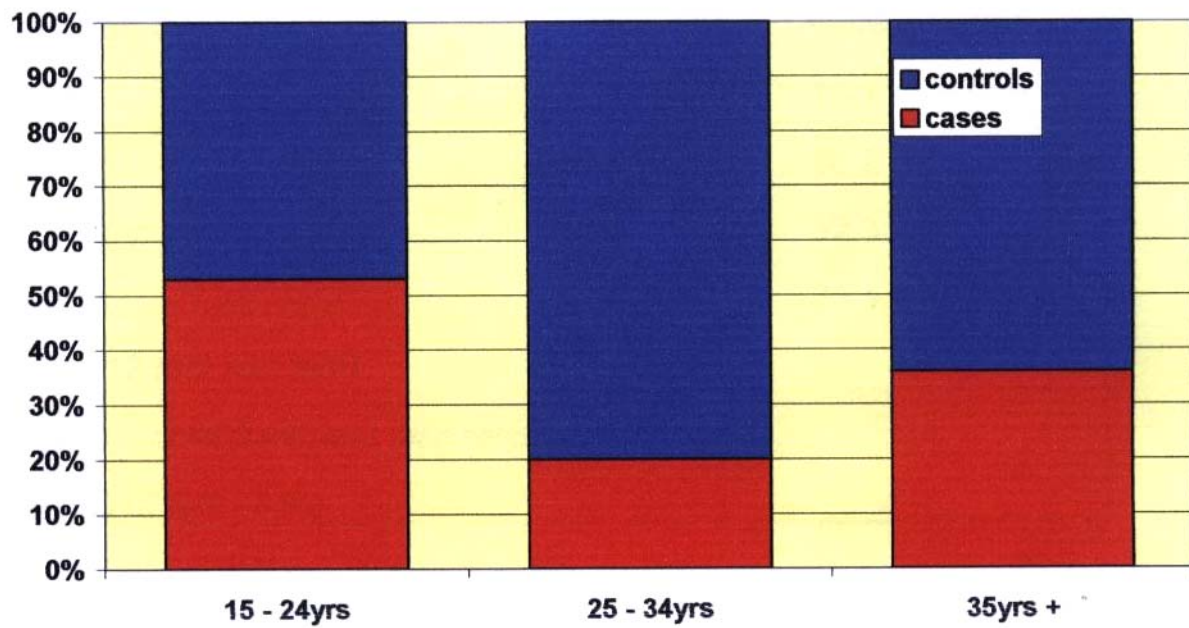
### **3.7. Previous history of stillbirth:**

It is shown in **Table 6** and **Figure 6** that there was a strong association between having a NTD baby and previous stillbirth delivery i.e. 54.8% in the cases contrasting to 12.9% in the control group. The relative risk was 3.3 and is highly significant ( $p < 0.0001$ ).

**Table 4: Maternal Age for cases (n=63) and for controls (n=125)**

<b>Age group</b>	<b>Cases (%)</b>	<b>Control (%)</b>
< 5yrs	0	0
15 -24 yrs	55.6	25.2
25 – 34 yrs	30.2	61.8
35 yrs+	14.3	13.0
Maternal age under vs. over 25 yrs P<0.0001		
Relative risk 2.3(95% CI1.5-3.4)		

**Fig. 3: MATERNAL AGE**  
**P<0.001**

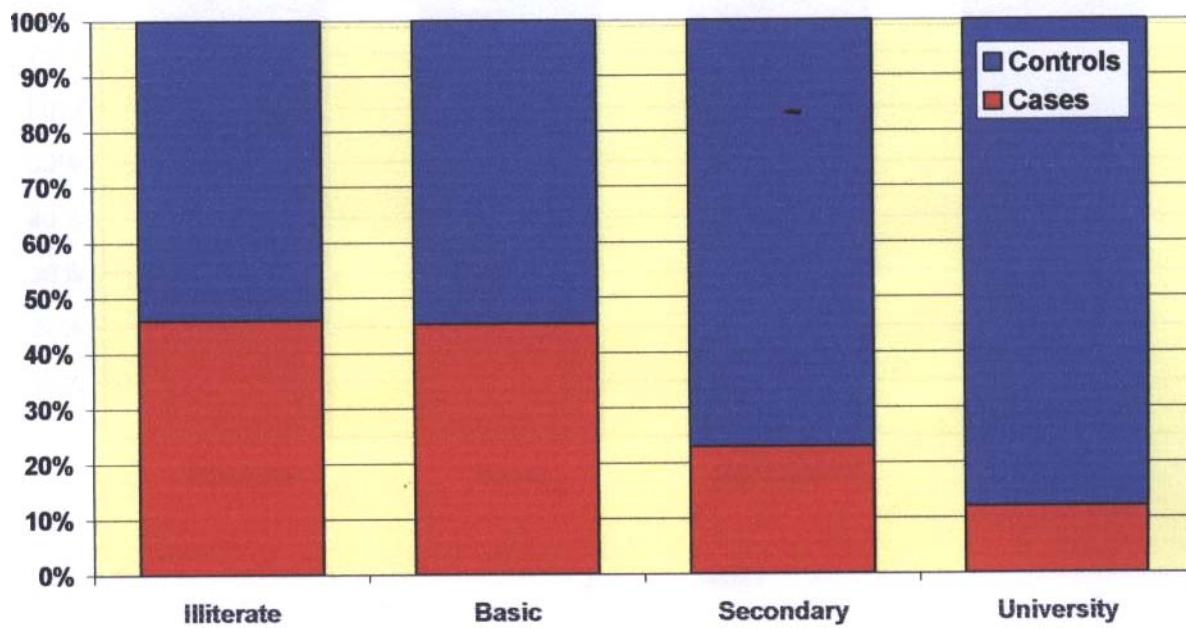


**Table 5: Maternal education for cases (n=63) and for controls (n=125)**

<b>Education level</b>	<b>Cases (%)</b>	<b>Control (%)</b>
Illiterate	27.4	16.1
Basic	46.8	28.2
Secondary	19.4	32.3
University	06.3	23.4
P<0.0012 (chi-square test)		
Relative risk of NTD with less than secondary education.		
2.42 (95% CI1.48-3.95)		

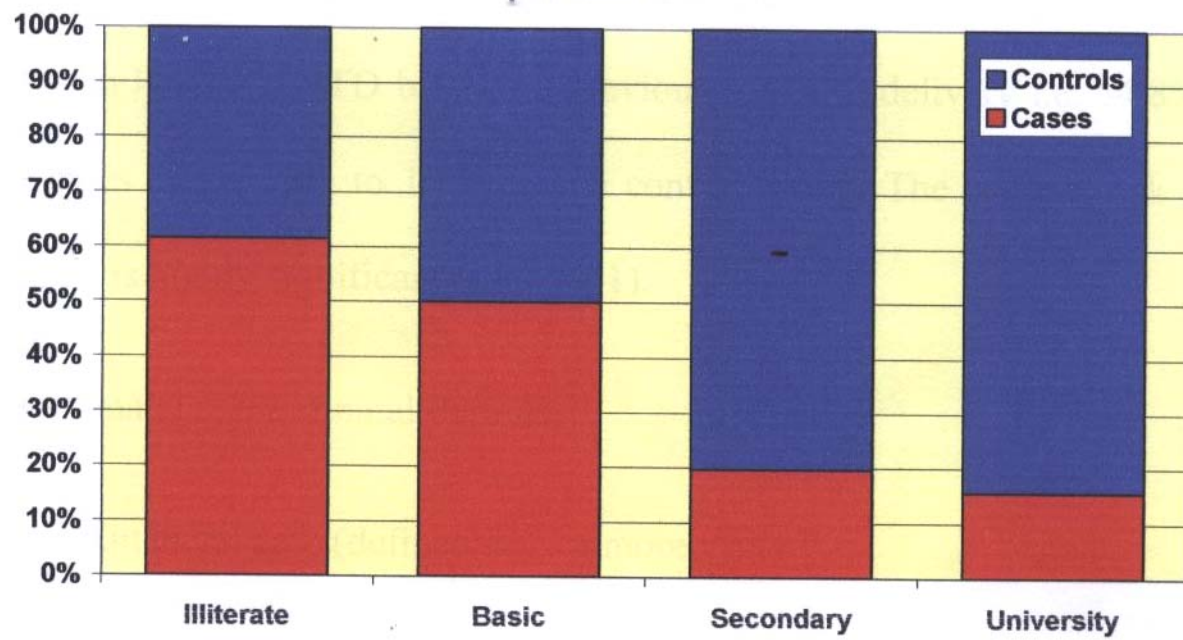


**Figure 4: MATERNAL EDUCATION:**  
**P<0.001**



**Figure 5: Paternal Education**

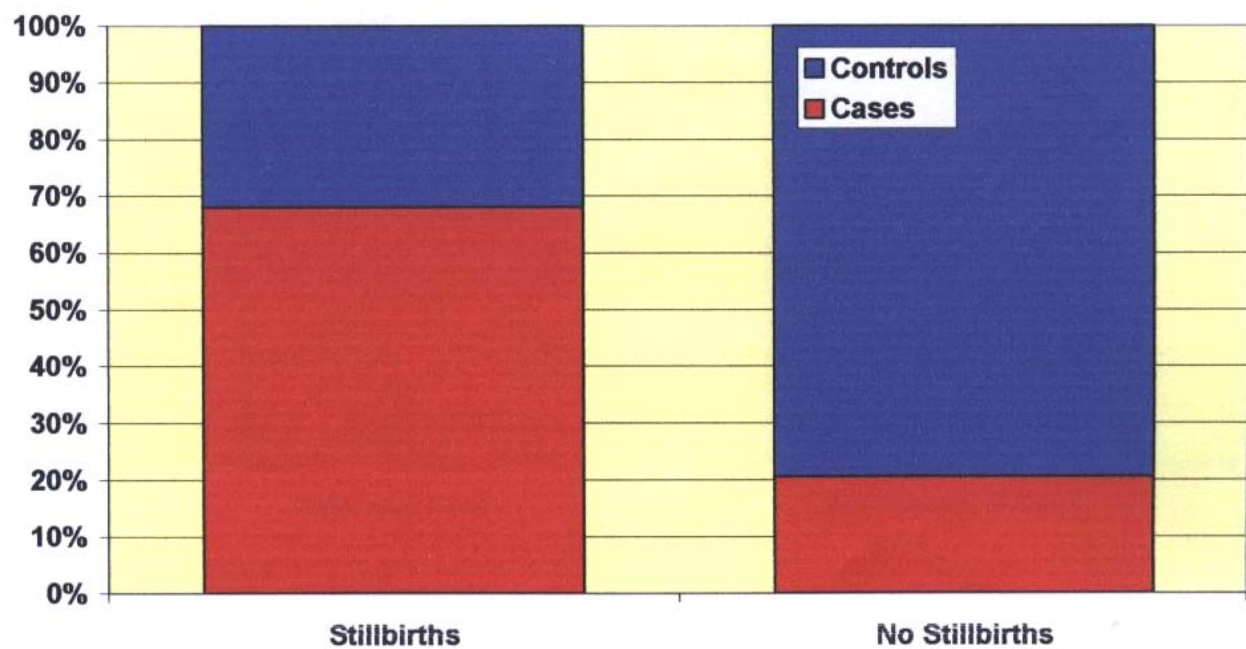
**P<0.001**



**Table 6: Previous history stillbirths for cases (n=63) and for controls (n=125)**

<b>Previous stillbirths</b>	<b>Cases (%)</b>	<b>Control (%)</b>
Yes	54.8	12.9
No	45.2	87.1
P<0.0001 (Fisher's exact test)		
Relative risk 3.30 (95% CI 2.26-4.83)		

**Fig. 6: PEVIOUS STILL BIRTH**  
**P<0.001 (RR3.3) -**



### **3.8. Prenatal and Perinatal Periods:**

#### **3.8.1: Antenatal care (defined as 2 or more visits):**

**Figure 7** shows that fewer antenatal visits were made by of NTDs; only 19 (30%) of mothers while most (70%) of the controls had antenatal care.

#### **3.8.2: Maternal previous medical illness:**

Only one (1 .5%) mother from the case group and 4(3%) mothers from the case group had previous medical problem ( $p=0.1$  (ns)).

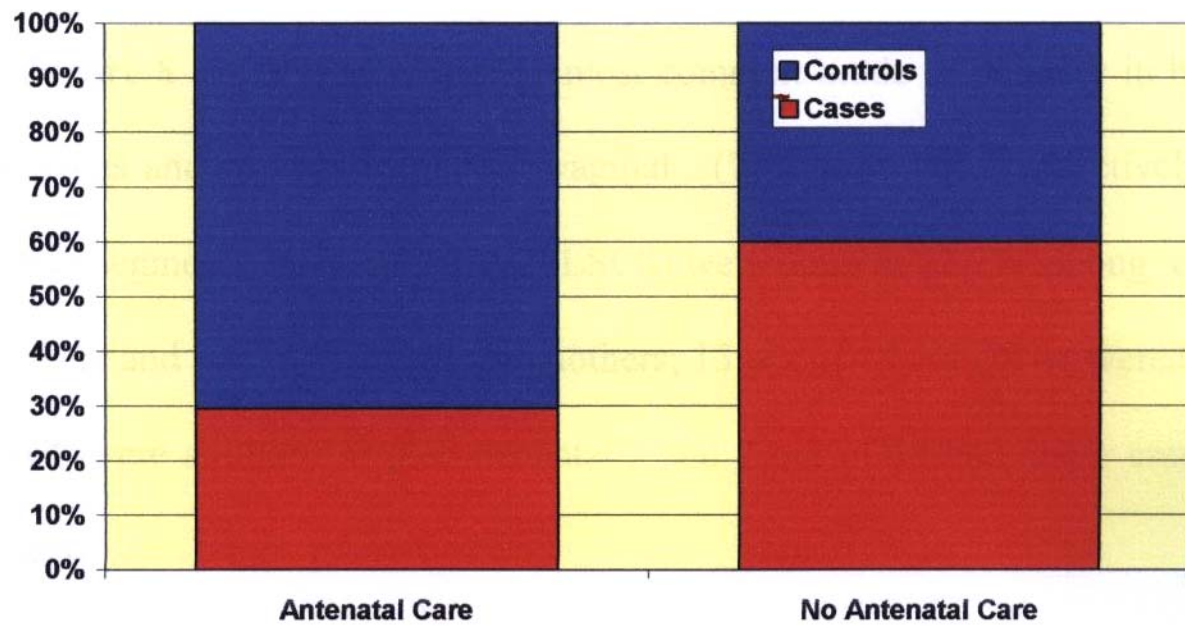
#### **3.8.3: Folic acid use before pregnancy:**

**Table 7** shows that no mothers either from the cases or control group had used folic acid preconceptually.

#### **3.8.4: Mode of delivery:**

In **Figure 8** : it is shown that the most common mode of delivery in both the cases and control group was vaginal . (77.8%and 76% respectively), Lower segment cesarean sections (LSCS) were done in 22.2% among case mothers and in 23.4%in control mothers; 13 out of 14 NTDS delivered by LSCS were stillborn or died neonatally and 7 out of 14 had major cranial defects.

**Figure 7: ANTINATAL CARE**  
**P=0.0054**



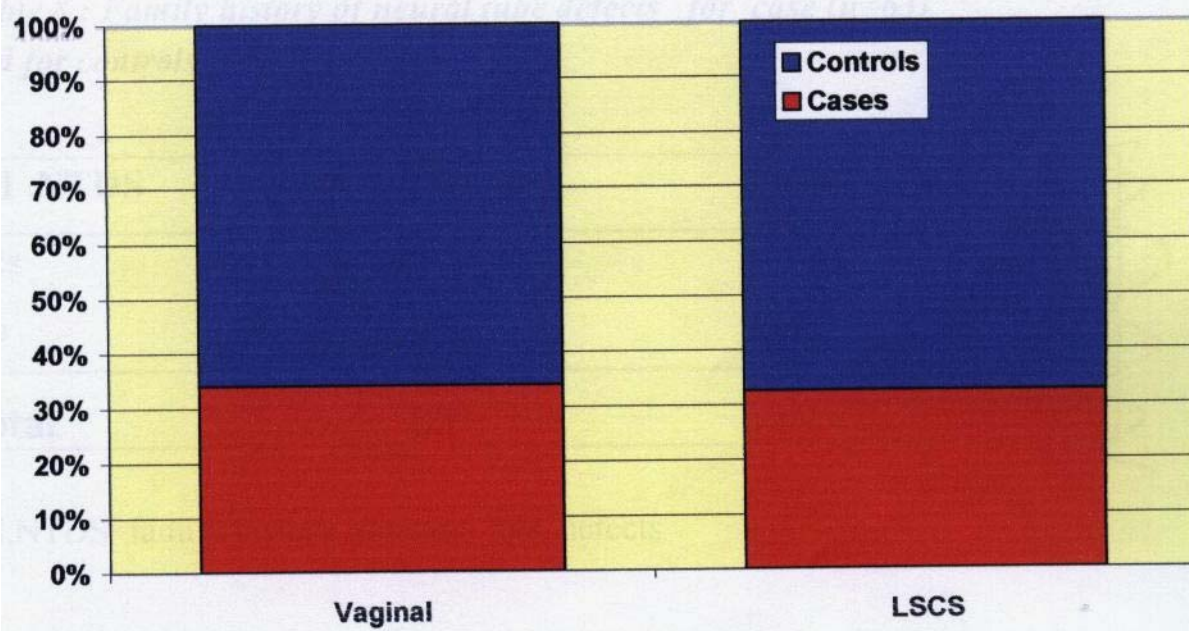
**Table 7: Folic acid use before pregnancy for cases (n=63) and for controls (n=125)**

	Cases (%)	Control (%)
F.A before pregnancy	0	0
No F.A before pregnancy	63	125

*F.A= Folic acid.*

**Figure 8: MODE OF DELIVERY**

**P=1**





### **3.9: Family history of NTDS:**

No family history of NTDs was found in the case group (0%) and the corresponding figure was 0.8% in the control group ( $p=0.1$  (ns)) (see **Table 8**).

### **3.10: Consanguinity:**

In figure 9 it is shown that there was no significant difference between cases and controls (23 from the cases, 40 from the controls ( $p=0.167$ )) as regard to consanguinity.

### **3.11: Previous child with neural tube defects or other congenital anomalies:**

No mother from either the case group ( $n=63$ ) or the control group ( $n=125$ ) had a previous child with NTD or other congenital anomalies.

### **3.12: Major consumption of Goats milk:**

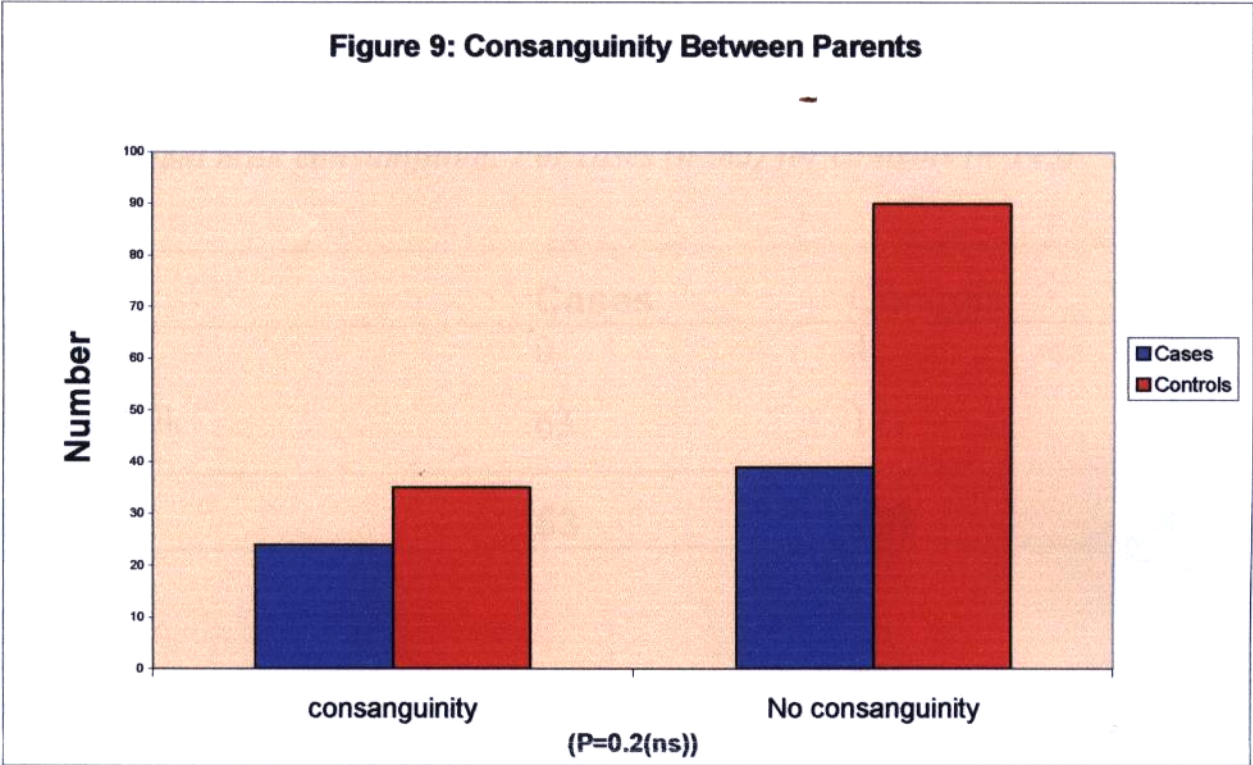
Table 9 shows no significant difference in goat milk consumption by the case mothers or the control mothers (5, 4 respectively). Antifolate drugs (e.g. Phenyton, Fansidar) use during pregnancy: was no case mothers who used antifolate drugs during pregnancy one control mother used them. ( $p=1$ ).

**Table 8: Family history of neural tube defects for cases (n=63) and for controls (n=125)**

<b>FH.NTDS</b>	<b>Cases (%)</b>	<b>Control (%)</b>
Yes	0	1
No	63	124
<b>Total</b>	<b>63</b>	<b>125</b>

*FH.NTDS= Family history of neural tube defects.*

**Figure 9: Consanguinity Between Parents**



**Table 9: Goat milk consumption for cases (n=63) and for controls (n=125)**

	<b>Cases (%)</b>	<b>Control (%)</b>
Goat milk	0	4
No goat milk	63	121
<b>Total</b>	<b>63</b>	<b>125</b>

### **3.14. Tribes and ethnic group:**

Table 10 shows that most of the cases (40) and the controls (80) were coming from tribes originating in the west of the country i.e. no significant difference between both groups ( $p=0.165$ )

**Table 10: Tribes and origins for cases (n=63) and for controls (n=125)**

<b>Tribe from</b>	<b>Cases (%)</b>	<b>Control (%)</b>
NORTH	13 (20.7	18 (14.4)
SOURTH	02 (03.1)	10 (08.00)
EAST	00 (0.0)	03(02. 3)
WEST	40 (63.5)	80 (64.0)
CENTER	08 (12.7)	14 (11.2)
<b>TOTAL</b>	<b>63 (100.0)</b>	<b>125 (100.0)</b>

P = 0.147 (ns)

## 4.1 DISCUSSION

The study has been conducted prospectively in a hospital based setting that is Omdurman Maternity Hospital; thus it may not reflect the actual condition in the community especially that a huge number of deliveries occur at home.

The incidence of NTDs during the study period from the first of February 2003 to the end of January 2004 was 3.48/1000. This is the highest incidence in Africa compared to that in Malawi 0.47/1000, Tunis (1.05/1000), South Africa (1.74/1000), Congo (0.12/1000) and Ghana (1.15/1000). It is almost approaching the highest incidence reported in Europe that occurred in Ireland (4/1000) and it is higher than the incidence in U.S.A (1/1000) (14-18,20,21,29).

Looking at the spectrum of NTDs, the study obviously reflected the severe end of the spectrum. This is recognized from the high anencephaly rate of 36.5% compared to 47.6% of spina bifida and adding to the severity is that most of the cases (80%) were either stillborn or died within the neonatal period. This is compatible to the findings in one study done in Malawi where most of the spina bifida cases ended lethally (14).

One of the very rare forms of NTDs appeared in this study, that is the iniencephaly (Figure D) which was reported in only one study done in

Northern China in 1995 where the number of the rare forms of NTDs was high(24 ).

The females outnumbered the males in this study (50 females: 10 males) with the male to female ratio of 1:5 .this is in agreement with most of the reports in the literature .In a study from Malawi, the male to female ratio was found to be 1:4, in another study in Cape Town the ratio was 0.89for spina bifida and 0.67 for anencephaly( 14-16).

Interestingly 20% of NTDS had other congenital anomalies. This high occurrence of associated congenital anomalies means that the syndromic type of NTDS which is elsewhere considered to be rare is rather common in our community, and this stimulates more concern about genetic factors in the causation of NTDs in Sudan , inspite of the fact that no single mother from either the case group or the control group had family history of NTDs or other congenital anomalies. The association with other congenital anomalies was reported in the study done in Tunis by Soumaya SG et al.( 15),however other operating environmental factors cannot be ruled out.

Another interesting point which could be considered in the causation of NTDs is the consanguinity especially there is much concern about the genetics of NTDs .A recent study from Ireland found the mutation encoding for the variant gene of the enzyme MTHFR and it also found that it causes



10 % of NTDs. (25). Sudan is known for the tradition of intermarriages in families but in this study no significant difference between cases and controls as regard to consanguinity.

The maternal age and the level of education of both parents were taken as indicators for the socioeconomic status. It is assumed that if the mother is young and the level of education is low, the socioeconomic status will be poor. As it is described in this study that most of the mothers were below 25 years of age with a relative risk of 2.3 i.e. there was a strong association between the younger age, NTDs, and both parents having poor educational background. This relationship was proved by Myer who compared the prevalence of NTDs in North Carolina (USA) from 1995 -2001 and found that when the maternal level of education and their socioeconomic status improved, the prevalence of NTDs decreased (29).

In this study there was a significant association between previous stillbirth delivery and NTDs this may throw more light on the severity of NTDs and put more questions about the cause of NTDs in our community.

The antenatal care was defined as 2 or more follow up visits during pregnancy. This study showed fewer mothers of cases had done antenatal care and accordingly they are more likely not to have done any ultra sound scans for the NTDs to be diagnosed. This might have led to the high

incidence of NTDs if it is accepted that termination of pregnancy can reduce the incidence as in some community like the U.K and U.S.A where if the screening tests (including U/S) revealed NTDs the pregnancy is immediately terminated. ( 30 ). Moreover absent antenatal care deprives the mother from being given the information about the antifolate agents that should not be taken during pregnancy although no mother from the case group claimed taking these drugs .Also during the antenatal visits any maternal illness that can be associated with NTDs such as Diabetes or hypertension can be controlled. Yet in this study no significant number in the case mothers had any medical problem during pregnancy.

A major intake of goats milk by the mother was postulated as a possible cause of folate deficiency as it is low in folate, but in this study no significant difference between cases or controls was found.

It is well proven by many studies all around the world that Folic acid use preconceptionally (either by taking a diet high in folate or by supplementation before pregnancy or by fortification of diet) can reduce the incidence of NTDs besides improving the general health of the population. This had lead the Food and Drug Administration in USA (FDA) in 1998 to mandate a national fortification of flour with folic acid to reduce the incidence of NTDs and studies done afterwards proved that folic acid works

in doing this. For example, the study done in a high prevalent area in Northern China where the incidence was 6/1000 and after folic acid supplementation the incidence was reduced to 2/1000. In this study no mother from the case or control group had any preconceptional folic acid supplementation and as they are of low socioeconomic status they were more likely to have a diet deficient in folic acid.

The study showed that most of the mothers (cases and controls) were delivered by the vaginal route but still there was 14 NTD case (22%) delivered by lower segment cesarean section (LSCS ). This seems unfair on the mother who is going to have an NTD baby to be subjected to the hazards and complications of the operation and this could be avoided by doing ultrasound scans at least just once during pregnancy. However this remains a controversial issue.

There is no mention in the literature that NTDs are concentrated in a certain ethnic population. The highest incidence of NTDs in Europe (4/1000) was in Ireland in a group of the population known to have Celtic origin but this high incidence was not due to genetic predisposition but because this group were known to eat a diet deficient in Folic acid. Most of the NTDs in this study came from tribes that have the west of Sudan as an original home but this was not significant since most of the controls were having the same

pattern and this could be explained by that following environmental and political issues, Omdurman city became highly inhabited by people coming from western Sudan. This issue of genetic predisposition remains to be answered by further research.

## 4.2. CONCLUSIONS

- The incidence of neural tube defects in Omdurman Maternity hospital during the year 2003-2004 was 3.48/1000.
- NTDs constituted about 59% of all congenital anomalies at birth.
- The male to female ratio was 1:5.
- The lesions of NTDs were severe with high stillbirth/ NND rate.
- NTDs accounted for 3.25/1000 live and stillbirths.
- The high association with other congenital anomalies leads to the consideration of genetic factors in the causation of NTDs in Sudan.
- Young maternal age, low educational level and previous history of stillbirth are strongly associated with NTD baby delivery.
- Antenatal care was poor in NTDs mothers.
- Most NTDs were not diagnosed before delivery.
- Failure of antenatal diagnosis possibly leads to inappropriate LSCS.
- There is still lack of evidence regarding the benefit of preconceptional use of folic acid in this study since none of the mothers of the cases or controls used this vitamin.

### **4.3. RECOMMENDATIONS**

- The high incidence of NTDs in Omdurman Maternity Hospital constitutes a major health problem. This invites a nationwide registry for all congenital anomalies.
- Improvement in antenatal care services is needed to assist in the early discovery of NTDs and accordingly to anticipate plans for the problem since termination of pregnancy is not acceptable in our community.
- It is known that prevention is better than cure. Since folic acid is proved to reduce more than 70% of NTDs if used preconceptionally it is recommended for the health and medical authorities to increase the public awareness about folic acid and its beneficial effects on the public health as general and on reducing a grave congenital anomaly like NTDs; and to promote a nationwide programs to supplement folic acid to all women in the child bearing age .In a country like Sudan, this could only be achieved by legislation leading to fortification of a staple diet like bread, salt or Sugar by folic acid.
- Further studies are needed to ascertain the incidence in the whole country and to disclose more informations about the cause of NTDs in Sudan.

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**University of Khartoum**  
**Faculty of medicine**  
**Department of pediatrics and child health**  
**Neural tube defects surveillance in Omdurman maternity**  
**hospital 20003-2004**

**Identification data:**

Date..... telephone number.....

Date of birth..... .

Sex of infant: male ☐ female ☐

Mother's age..... occupation.....

**Mothers level of education :**

Illiterate ☐ basic ☐ higher secondary ☐ university ☐

**Father age** ..... **Occupation**..... **monthly income** ....

**Father level of education:** illiterate ☐ basic ☐ higher secondary ☐  
university ☐

**Tribe** .....

**Family history of NTD:** yes ☐ No ☐

**Consanguinity:**

Yes ☐ No ☐

**Total live birth** ☐

**No of stillbirth** ☐

**No of infant /child deaths** ☐

**Previous history of NTD:** Yes ☐ No ☐

**Previous child with other congenital anomalies:** Yes ☐ No ☐

**Medical history:**

Diabetes ☐ hypertension ☐ others ☐

**Current pregnancy:**

ANC: Yes ☐ No ☐

U/S: yes ☐ No ☐

Preconceptional folate: yes ☐ No ☐

Post conceptional folate: yes ☐ No ☐

Antifolate agents: yes ☐ No ☐

Drinking goats milk in large amounts: Yes ☐ No ☐

First HB% ☐ done on ☐ weeks gestation

**Delivery:** S.V.D ☐ assisted ☐ c/s ☐

## Examination sheet

Alive ☐ stillbirth ☐

Gestational age ☐ wks

Wt ☐ kg head circumference ☐ cm length ☐ cm

**Lesion:** anencephaly ☐ encephalocele ☐ open meningocele

☐ open myelomeningocele ☐

Others uncertain ☐

**Level of lesion:** cervical ☐ thoracic ☐ lumbar ☐ sacral

☐ lumbosacral ☐ thoracolumbar ☐ -

**Association with hydrocephalus:** yes ☐ No ☐

**Lower limbs:** no movement ☐ little movement ☐

abnormal neurology ☐ normal ☐

**Other neurological abnormality:** describe

### Musculoskeletal

Club foot ☐ dislocated hip ☐ others ☐

**Sphincters:** patulous ☐ spastic ☐ normal ☐

### General examination

C.VS

Respiratory

Abdomen

Genitourinary